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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

DEC 7 1995
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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP# 4F04407. Sulfentrazone, F8426 and F3686. Letter of 11/9/95. Barcode D221381. CBTS# 16577.

FROM: G.F. Kramer, Ph.D., Chemist
Tolerance Petition Section I
Chemistry Branch I, Tolerance Support
Health Effects Division (7509C)

THRU: R. Quick, Section Head
Chemistry Branch I, Tolerance Support
Health Effects Division (7509C)

TO: JoAnne Miller, Product Manager
Dianne Morgan, Team 23 Reviewer
Registration Division (7505C)

FMC has submitted an application for permanent tolerances for the combined residues of the herbicide sulfentrazone (N-[2,4-dichloro-5-[4-(difluoromethyl)-4,5-dihydro-3-methyl-5-oxo-1H-1,2,4-triazol-1-yl]phenyl]methanesulfonamide) and its major metabolite 3-hydroxymethyl sulfentrazone (N-[2,4-dichloro-5-[4-(difluoromethyl)-4,5-dihydro-3-hydroxymethyl-5-oxo-1H-1,2,4-triazol-1-yl]phenyl] methanesulfonamide). The end use product, Authority 75DF Herbicide, is to be registered for use on soybeans.

On 10/25/95 and 10/27/95, representatives of FMC and CBTS discussed issues related to our previous review (Memo, G. Kramer 9/19/95). Issues pertaining to two products in development, F8426 and F3686, were also discussed. FMC has submitted their minutes of the conversations for our review. We find these minutes to be an accurate summation of the conversations and to be consistent with Branch Policy.

Attachment: 11/9/95 Letter from Linda Froelich (FMC) to G. Kramer

cc (with attachment): PP#4F04407, Kramer, Circ., R.F., S.F.
RDI: R. Quick (12/5/95), R.A. Loranger (12/6/95), M.S. Metzger (12/7/95)
G.F. Kramer:804V:CM#2:(703)305-5079:7509C:CBTS

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Facsimile Cover Sheet

FMC CORPORATION
Agricultural Products Group
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To:	**Dr. George Kramer**
Company:	**EPA**
Phone:	**703-305-5079**
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From:	**Linda Froelich**
Company:	**FMC Corporation**
Phone:	**609-951-3486**
Fax:	**609-951-3670**
Date:	**11/9/95**
Pages including cover page:	**6**

Dear Dr. Kramer,

Thank you for taking the time to speak with John Becker and me on our questions and issues regarding sulfentrazone, F8426, and F3686. We very much appreciate the comments and suggestions you made during our telephone conference calls on 10/25/95 and 10/27/95.

Attached are the questions we discussed and our understanding of your responses. Please review and if you have any corrections and/or changes please write them on the document. We are requesting that the signed copy be faxed back to me at 609-951-3670.

Again, thank you for your time and the guidance you gave us. Please call me if you have any questions or require additional information.

Sincerely,

Linda W. Froelich

Linda W. Froelich
Program Coordinator
Developmental Chemistry

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Radiovalidation for Sulfentrazone (from 10/25/95 discussion)
Conclusion 5b. (from Oct. 12, 1995 EPA Sulfentrazone Review; PP# 4F4407, CBTS 15851)

1) Q: Since there is no (residue) method established for barley, how do you envision the radiovalidation for this crop being done? Should the wheat method be used?

   A: Yes. Since barley is the surrogate for the grain crops and the methodology is similar for the rotated crops, barley should be analyzed through the residue method for wheat.

2) Q: FMC is intending to conduct the radiovalidation on barley forage only, do you concur? Forage would provide the most reliable quantitative comparison due to the level of residues found in the metabolism study. Grain has no residues, and straw is not as relevant as a feeding crop.

   A: Yes. Since grain has no residues, forage should be done, especially if the method is the same.

3) Q: Since methodology for the des,des-sulfentrazone is a separate procedure with iodomethane, and des,des was greater than 10% TRR only in barley forage, do you feel radiovalidation for this analyte is needed? Will the Agency consider this analyte as part of the tolerance expression for wheat forage?

   A: Radiovalidation for this analyte probably would not be needed as long as it isn't part of the tolerance expression. As long as des,des is not considered or believed to be more toxic than parent, it is unlikely to be of a concern for a tolerance expression.

4) Q: Considering the crop difference (barley vs. wheat) and the potential for marginal recoveries, we would like general clarification on what constitutes "validation". Is an analysis to demonstrate that the analytes of concern are qualitatively recovered adequate? OR Must we demonstrate a quantitative similarity to the Metabolism study for each analyte of concern? How close must the Residue and Metabolism values compare? Are there any EPA evaluation criteria or guidance here?

   A: A qualitative assessment of extractability is really no longer adequate. A quantitative assessment is expected and the margin of comparison (Residue value vs. Metabolism value for each analyte) is about ±20%. This is similar to the acceptable method recovery range of 70-120%.

5) Q: Does the Agency have any general guidance on the extent and circumstances for doing radiovalidation? Is the Agency going toward radiovalidation for each crop that has a Metabolism study? Previously, it has been acceptable to demonstrate that the extraction scheme for the residue method could remove in situ residues from the matrix.

   A: The Agency does not expect radiovalidation on every crop that has ^{14}C samples. The focus is still on the method. For example, one radiovalidation can be done on one method covering several crops/matrices as long as the residue method is the same. I (Dr. Kramer) am not aware of any specific guidance on conducting radiovalidation studies, but will follow-up and ask some of the Branch Senior Scientists. (During our 10.27 discussion: There is no specific

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guidance on radiovalidation but the Agency concurs that more should be provided. This additional guidance may be incorporated into the revised Residue Chemistry guidelines.)

Additional Sulfentrazone questions (from 10/27/95 discussion):

1) Q: In regard to the rice rotation studies, the term "quantifiable residues" has been applied to the total straw residue of 0.073 ppm, which is the maximum sum of 3 analytes. However, in this case no individual analyte exceeded the proven limit of quantitation for that analyte. The sum total does exceed the individual analyte LOQ of 0.05 ppm. How does the Agency define and apply the term "quantifiable"?

   A: The Agency defines "quantifiable" as the level at which residues can be accurately determined and proven. Typically this is the method LOQ and is determined on an analyte-to-analyte basis. However, "quantifiable" may be below the method LOQ if the LOQ has been arbitrarily set too high and residues could be quantitated at lower levels. In this specific case, additional chromatograms and justification may be submitted for review and the situation can be re-evaluated.

2) Q: The term "significantly different" in regard to conducting additional independent method validation studies is vague. In previous meetings, the Agency has suggested that changes in the detection system for the analytical method could constitute a "significant change". Is this true? For example, would a change from GC-ECD to GC-MSD be considered significant?

   A: In this case, provided the extraction and clean-up methodology was the same, going from a general detector such as ECD to a more specific detector such as MSD would not be significant. However, going from MSD to ECD would require validation to prove that the less specific detection system was still valid.

F8426:

1) Q: The major metabolites found in the F8426 wheat and corn metabolism studies are shown in the tables on the following page (note there are no residues in grain). We analyzed for these major metabolites in the RAC and processing trials (submitted for the EUP/TT) and found no quantifiable residues. The methodology is difficult and we would like to use a modified approach for the remainder of the crop RAC trials. FMC would like to propose to start the extraction procedure with an acid hydrolysis which converts parent to chloropropionic acid and analyze for the combined residues of parent and chloropropionic acid plus desmethyl chloropropionic acid. This will bracket the hydroxymethyl metabolite which is difficult to analyze because it involves separate derivatization. It should all be moot since what we have found in the trials to date is no quantifiable residues. Do you agree with this approach?

   A: This is difficult to answer without a review by the Metabolism committee who would determine if the hydroxymethyl chloropropionic acid metabolite is toxicologically significant. Assuming that it is not, then follow your approach for analyzing the remainder of the trials. Keep the samples in the freezer so they could be checked later for the hydroxymethyl metabolite, if necessary. Acid hydrolyzing parent to chloropropionic acid and then analyzing for chloropropionic acid and desmethyl chloropropionic acid is fine.

2) Q: Since the results of the RAC trials for corn (6 RAC plus one processing study) and wheat (2 RAC plus 1 processing) show no quantifiable residues, can we analyze 25% fewer trials for these two crops (15 vs 20 trials) as long as there is adequate geographic distribution?

   A: Yes. However, if you see any quantifiable residues then you must do all 20 trials.

3) Q: The ^{14}C soybean metabolism study results showed there are no residues in the bean (TRR <0.001 ppm). The highest TRR in forage and hay was 68 ppb (hay) which consisted of parent, chloropropionic acid and hydroxymethyl chloropropionic acid. Based on these results and since we will restrict feeding of forage and hay, do we need a soybean tolerance at all? Do we need any RAC trials?

   A: Yes, to both. RAC trials and a soybean tolerance are necessary to cover any possible misuse of the chemical.

4) Q: If RAC trials and a tolerance for beans only are needed, FMC proposes to use chloropropionic acid as the marker residue for itself and parent following acid hydrolysis. Do you concur? What about a parent only tolerance?

   A: Using chloropropionic acid as the marker residue is fine and then have a parent plus chloropropionic acid tolerance. EPA likes this kind of approach and would like registrants to try to have the same methods for different crops and matrices, if possible.

5) Q: If we need to prove that there are no residues in a field situation, then we should be able to do 25% fewer soybean trials based on the expectation of no quantifiable residues. Is this correct?

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A: Yes, and again, if you see any quantifiable residues then you need to do all 20 trials.

6) Q: In a situation as described for soybean seed, where no residues are expected, what do you recommend as the marker analyte(s) for a storage stability study? Parent only? Is a storage stability study needed at all?

A: A storage stability study is needed with the same analytes looked for in the RAC trials - parent and chloropropionic acid (spiked separately but analyzed together).

Summary of ^{14}C-F8426 Major Metabolites in Wheat Forage and Straw

Commodity / Metabolites	Forage				Straw			
	Phenyl Label		Carbonyl Label		Phenyl Label		Carbonyl Label	
	TRR %	ppm	TRR %	ppm	TRR %	ppm	TRR %	ppm
3-OH-F8426-ClPAc	16.6	0.023	17.0	0.021	12.7	0.031	11.6	0.026
DesMe-F8426-ClPAc	14.2	0.019	13.9	0.017	9.5	0.023	10.0	0.025
F8426-ClPAc	5.5	0.008	5.8	0.007	3.6	0.009	0.6	0.001
F8426	1.6	0.002	2.0	0.002	1.4	0.003	1.7	0.004

Summary of ^{14}C-F8426 Major Metabolites in Corn Forage, Silage and Fodder

Commodity / Metabolites	Forage				Silage				Fodder			
	^{14}C-Phenyl		^{14}C-Carbonyl		14C-Phenyl		^{14}C-Carbonyl		^{14}C-Phenyl		^{14}C-Carbonyl	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
DesMe-F8426-ClPAc	23.1	0.007	18.8	0.010	27.2	0.016	15.5	0.004	24.2	0.065	32.1	0.033
F8426-ClPac	12.8	0.004	10.8	0.006	10.5	0.006	9.6	0.003	8.8	0.024	8.2	0.008
F8426	29.8	0.009	36.5	0.020	17.9	0.010	12.6	0.003	20.5	0.055	10.0	0.010

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F3686:

1) Q: F3686 is a nonselective herbicide applied to existing weeds prior to emergence of any crop (similar to paraquat or glyphosate). It potentially could be used in this manner prior to the planting of many crops. What are the rules for selecting crops on which to conduct metabolism studies in such a case where there is no expectation of uptake of TRR? Do we do a monocot, dicot and root crop? We can stop with these 3 studies if they show similar profiles (even if that profile shows no 14C uptake), correct? Can we do less?

   A: Do representative monocot, dicot and root crop studies and if they show similar metabolic profiles or no uptake you can stop. You cannot do less than that for use on many crops.

2) Q: If we want to register this compound for soil application to existing weed cover in orchard and vine crops, would we need additional metabolism studies on a representative species? Even if the three studies in question #1 show similar profiles?

   A: If there is no uptake in the three studies in question #1, then you wouldn't need to do any additional metabolism studies. Even if there is uptake, I doubt that additional studies would be needed.

3) Q: This product also has potential utility as a cotton defoliant. Application would be to mature foliage just prior to harvest. Is it necessary to do a plant metabolism study for such a use? Would the dicot study mentioned in question #1 qualify? If, in the future there were additional foliar uses (ex. potato defoliant), would there need to be separate metabolism studies done? Another three (monocot, dicot, root crop) for foliar uses?

   A: The dicot study in question #1 would not qualify since it would have been done with a different use pattern (soil vs foliar application). Therefore, a cotton metabolism study would be necessary to determine how the compound is metabolized from a foliar application. This is why EPA requires confined rotational crop studies since different metabolites may be formed in the soil which can then be taken up by the plants and metabolized. A potato metabolism study would not be necessary as the cotton metabolism study would cover both. If, however, there were going to be additional foliar uses, then separate monocot, dicot and root crop metabolism studies would be required.

4) Q: If there is no expectation of residues demonstrated in the representative metabolism studies, must we do residue studies on every crop on which we want to register?

   A: As it stands now, yes, since there are only two categories of use - food and non-food. If no quantifiable residues are confirmed in the field studies, then 25% fewer trials will be adequate. However, there are discussions on-going at EPA about adding a third category - food-use with no expectation of residues. This may have impact on what residue studies you do for this compound. I will follow-up with my colleagues on this issue.

George Kramer, Ph.D. 12-7-95 Date

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